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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/815,262	ENGELHARDT ET AL.	
	Examiner	Art Unit	
	Kevin K. Hill, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-60* is/are pending in the application.

4a) Of the above claim(s) *3,25-27,29-42,45,51-53 and 55-59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-24,28,43,44,46-50,54 and 60* is/are rejected.

7)☒ Claim(s) *1-2, 9-15, 17-20 and 43-44* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. Applicant's response to the Requirement for Restriction, filed on March 19, 2007, is acknowledged.

Applicant has elected the invention of Group I, Claims 1-32 and 43-60, drawn to a method of enhancing recombinant adeno-associated virus (rAAV) transduction in mammalian cells, comprising contacting the mammalian cells with at least one agent in an amount effective to additively or synergistically enhance rAAV transduction.

Within Group I, Applicant has further elected the restricted subgroup "A", wherein the at least two agents additively enhance rAAV transduction.

Within Group I, Applicant has elected the following species:

a) the agent interaction effect species "ii), wherein the agent alters cellular uptake of rAAV, as recited in Claims 4 and 46.

b) the biological functionality associated with an agent species "vi", wherein the agent modulates rAAV processing in the cell, as recited in Claims 28, 43 and 54.

c) the agent category species "xiii and xiv", wherein the agents are an antibiotic and a chemotherapeutic, as recited in Claims 8 and 47.

d) the biological functionality species "doxil" and "LLnL", as recited in Claims 21 and 60. However, upon further examination of the subject matter, the Examiner has extended the species under examination to include doxorubicin.

e) the cell type species "mammalian lung cell", as recited in Claims 16 and 48.

f) the polypeptide biological functionality species "cystic fibrosis transmembrane conductance regulator (CFTR)", as recited in Claim 20, wherein CFTR is found in both rAAVs.

2. Election of Applicant's invention(s) was made with traverse.

Applicant did not provide arguments regarding the restriction between Group I and Group II. Because Applicant did not distinctly and specifically point out the supposed errors in the Group restriction requirement, the election has been treated as an election without traverse

and the restriction and election requirement is deemed proper and therefore made final (MPEP § 818).

With respect to the restricted subgroup and species elections within Group I, Applicant argues that:

a) the practice of restriction requirement is optional in all cases,

b) the Group IA invention wherein the at least two agents additively enhance rAAV transduction is closely related to the Group IB invention wherein the at least two agents synergistically enhance rAAV transduction, e.g. both inventions are classified in the same class and subclass, and

c), the species election requirements are improper because they do not take into consideration the claimed invention, i.e. the use of certain agents to enhance AAV transduction, wherein the use of the agents are not limited to the cell type to be transduced or the gene(s) to be delivered by the AAV.

Applicants' arguments have been fully considered but are not found persuasive.

With respect to a), MPEP §803 states that "If the search and examination of all the claims in an application can be made without serious burden, the Examiner must examine them on the merits, even though they include claims to independent or distinct inventions."

In the instant case a serious burden exists since each limitation, directed to how each agent mechanistically affects the cell biology of the target cell requires a separate, divergent, and non co-extensive search and examination of the patent and non-patent literature. For instance, a search and consideration of the prior art as it relates to the regulation of microtubules or microfilaments would not be adequate to uncover prior art related to rAAV processing in the cell.

With respect to b), a search and examination of all the claims directed to both embodiments involves different considerations of novelty, obviousness, written description, and enablement for each claim. The Examiner has previously explained that the functional interaction between two structurally distinct and unrelated agents cannot be predicted *a priori* to be additive, synergistic, or have no detectable interaction. In view of these requirements, it is the

Examiner's position that searching and examining all of the claims including limitations to additive and synergistic in the same application presents a serious burden on the Examiner for the reasons given above and in the previous Restriction Requirement.

With respect to c), it is noted that should Applicant traverse the species election requirement, that Applicant was invited to submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. Although Applicant has created a genus of structurally and functionally distinct compounds as per their instantly disclosed shared property, specifically that the agents may be employed to enhance AAV transduction, Applicant has not clearly admitted on the record that these agents are obvious variations of each other.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 3, 25-27, 29-42, 45, 51-53 and 55-59 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

4. Claims 1-2, 4-24, 28, 43-44, 46-50, 54 and 60 are under consideration.

Priority

5. Applicant's claim for the benefit of a prior-filed application parent provisional application 60/459,323, filed on March 31, 2003 and 60/512,347, filed on October 16, 2003 under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

Information Disclosure Statement

Applicant has filed Information Disclosure Statements on July 29, 2005 and October 6, 2005, providing more than 200 references. The Examiner was able to consider these to the extent of time allowable and requests the Applicant to distinctly identify by page and line number with

a concise explanation of relevance any statements within a citation directly applicable to the instantly claimed invention. The signed and initialed PTO Forms 1449 are mailed with this action.

Specification

6. **The disclosure is objected to because of the following informalities:**

35 U.S.C. 112, first paragraph, requires the specification to be written in "full, clear, concise, and exact terms." The specification is replete with terms which are not clear, concise and exact. The specification should be revised carefully in order to comply with 35 U.S.C. 112, first paragraph. Examples of some unclear, inexact or verbose terms used in the specification are: The specification uses the terms "doxorubicin", "doxyrubicin" and "doxil", each of which may be abbreviated as "DOX". However, the specification discloses that doxil could not be confirmed to be bioavailable to cell culture cells (pg 80, lines 17-18; pg 82, lines 2-4), and that "intranasally doxil-treated mice did better than the doxorubicin-treated animals" (pg 110, lines 17-19). Thus, one of ordinary skill in the art would reasonably conclude that the functional ability(ies) of "doxorubicin", "doxyrubicin" and "doxil", are not identical in effect. As such, it is imperative that "doxorubicin", "doxyrubicin" and "doxil" be clearly and explicitly identified throughout the disclosure.

A) The use of trademark compositions has been noted in this application. Doxil is a registered trademark name, DOXIL®, and represents a liposomal formulation of doxorubicin. Similarly, the specification uses the term "Dowanol" and "Miglyol" (pg 54, lines 20-25) which are also registered trademarks. Trademarked compositions should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. Applicant is advised to review the specification to correctly identify all trademark compositions.

B) The units (DF* and mU) categorizing the results in Table 2 (pg 84) are not defined in the table or disclosed in the working example that describes the experiment used to acquire the data (Example 3), thus prohibiting a meaningful evaluation on the merits.

C) The specification discloses that Figure 4B tabulates luciferase activity in HeLa cells infected rAAV, "and co-administration of..., or a combination of LLnL and doxorubicin" (pg 19, lines 26-30). However, none the figure legends of Figures 4A-E identify data from the combined use of LLnL and doxorubicin.

D) Figure 6 consists of three panels, A-C. However, the specification does not disclose the data presented in Figure 6C (pg 20, lines 6-10).

E) Figures 7A-C are not adequately disclosed (pg 20, lines 11-12) for not identifying the "DOX" compound or the "RLU" that is being measured.

F) Figure 8 consists of three panels, A-C. However, the specification does not disclose which data is presented in its corresponding panel (pg 20, lines 13-16).

G) Figure 9 consists of four panels, A-D. However, the specification does not disclose which data is presented in its corresponding panel (pg 20, lines 17-23).

H) Figure 10 consists of two panels, A-B. However, the specification does not disclose which data is presented in its corresponding panel (pg 20, lines 24-29).

I) Figure 11 consists of four panels, A-D. However, the specification does not disclose which data is presented in its corresponding panel (pgs 20-21, joining ¶).

J) Figure 13 consists of two panels, A-B, wherein the specification discloses the data presented in the corresponding panels as "right panel" and "left panel". (pg 21, lines 18-23) However, there are no "right" or "left" panels. It would be remedial to correctly identify each panel by its Figure title: Figure 13A, Figure 13B. Furthermore, the "indicated drug combinations" are not adequately disclosed for not identifying the "DOX" compound.

K) Figure 17 consists of five panels, A-E. However, the specification does not disclose which data is presented in its corresponding panel (pg 22, lines 18-31). Furthermore, the description does not adequately identify the "DOX" compound.

L) The specification does not adequately identify the "DOX" compound whose effects are graphed in Figure 18 (pg 23, lines 2-5; pg 105, Example 7C).

M) The specification does not adequately identify the "DOX" compound whose effects are graphed in Figure 19 (pg 23, lines 6-11; pg 106, Example 7C).

Appropriate correction is required.

Claim Objections

7. **Claims 2, 9-15, 17-20 and 44 are objected to because of the following informalities:**

With respect to Claims 2, 9-15, 17-20 and 44, the claims recite structural features of the rAAV vector. However, the instant invention is drawn to methods of enhancing viral transduction of a mammalian cell, not a product. Absent evidence to the contrary, the recited structural elements of the rAAV vector are not germane to the claimed method because such elements play no role in the artisan-actuated method steps to enhance viral transduction into a host target cell.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. **Claims 1-2, 4-24, 28, 43-44, 46-50, 54 and 60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.** The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed to a method for enhancing recombinant adeno-associated virus (rAAV) transduction of a mammalian cell. At issue for the purpose of written

description requirements, are a) the identity and structure of the agent that "alters cellular uptake of rAAV", and b) the identity and structure of the agent that "modulates rAAV processing in the cell". It is noted that with respect to Claim 4, the recited agent that alters cellular uptake of rAAV is an undisclosed third agent to be used in the claimed method, wherein the elected first and second agents are DOXIL® and LLnL.

When the claims are analyzed in light of the specification, instant invention recites/encompasses a genus of structurally diverse compositions that are known in the art to possess mechanistically distinct biochemical activities. The lack of written support in the specification regarding the biological function possessed by each contemplated composition so as to be used in the instantly claimed method will be addressed presently.

> *Vas-cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not clearly allow persons of ordinary skill in the art to recognize that (he or she) invented what is claimed." (See *Vas-cath* at page 1116).

With respect to agents capable of altering the cellular uptake of rAAV, in analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, DOXIL® is the only species whose complete structure is disclosed to perform such functions. Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, no other identifying characteristics identify *a priori* an agent that would perform the claimed function.

With respect to agents capable of modulating rAAV processing in the cell, in analyzing whether the written description requirement is met for genus claims, it is first determined

whether a representative number of species have been described by their complete structure. In the instant case, LLnL, a proteosome inhibitor, is the only species whose complete structure is disclosed to perform such functions. Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, no other identifying characteristics identify *a priori* an agent that would perform the claimed function.

The specification does not disclose any identifying characteristic as to how an artisan would have differentiated a first agent from any other second or third agent so as to alter the cellular uptake of rAAV or modulate intracellular viral processing. It is noted that all these agents vary greatly in structure and function and therefore each represents a subgenus. Again, the members of any of the subgenuses themselves would have very different structure and the specification does not provide any description of any identifying characteristics of the species of the subgenuses

> The Revised Interim Guidelines state:
> "The claimed invention as a whole may not be adequately described if the claims require an essential or critical element which is not adequately described in the specification and which is not conventional in the art" (col. 3, page 71434), "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus", "in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (col. 2, page 71436).
>
> An Applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

Possession may also be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the Applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 1 19 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998), *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997)*, *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. See *Fiers v. Revel*, 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. *In Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

The two species of agents specifically disclosed to perform the claimed functions, DOXIL® and LLnL, are not representative of the genus of agents having distinctly different cell biological activities because the genus is highly variant. Accordingly, given that the specification does not teach what is the complete structure of a single species of the exceptionally broadly-defined "agent" genus that is explicitly disclosed to perform the recited functions, specifically i) alter cellular uptake of rAAV, and ii) modulate rAAV processing in the cell, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that the Applicant is in possession of the required starting materials to perform the necessary active steps and effect the claimed method, at the time the application was filed.

Thus, for the reasons outlined above, it is concluded that the claims do not meet the requirements for written description under 35 U.S.C. 112, first paragraph. Applicant is reminded

that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

9. **Claims 1-2, 4-24, 28, 43-44, 46-50, 54 and 60 are rejected under 35 U.S.C. 112, first paragraph**, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2ds 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Breadth of the Claims and The Nature of the Invention

The breadth of the claim is exceptionally large for encompassing methods of enhancing the transduction of an enormous genus of recombinant adeno-associated viruses (rAAV) to an enormous genus of mammalian cells (both organisms and physiological cell types), wherein the transduction may occur *in vitro*, *ex vivo* or *in vivo*, the method comprising the use of an enormous genus of structurally diverse agents recited to perform a broad genus of distinctly

different cell biological effects so as to enhance rAAV transduction in the target cell. Applicant broadly contemplates the term 'viral transduction' to include a broad genus of distinctly different and mutually exclusive cell biological processes, such as endocytosis, trafficking and processing of the rAAV through intracellular compartment(s), e.g., endosomal compartments, decreased viral nucleic acid or protein degradation, increased viral uncoating, or increased nuclear transport of virus or the viral genome, agents that interact with cytoskeletal elements, e.g., microtubules or microfilaments (pg 8, lines 23-27).

The inventive concept in the instant application is that rAAV transduction of a mammalian host cell may be enhanced by administering one or more compounds, e.g. the proteosome inhibitor LLnL or the antibiotic/chemotherapeutic compound doxil.

The State of the Prior Art, The Level of One of Ordinary Skill and The Level of Predictability in the Art

The level of one of ordinary skill in the art of recombinant adeno-associated viral vector design and delivery is considered to be high.

The prior art teaches that most viral gene delivery systems utilized to date have demonstrated significant limitations in practicality and safety due to the level and duration of recombinant transgene expression as well as their induction of host immunogenicity to vector proteins. (Kapturczak et al, Curr. Mol. Med. 1:245-258, 2001; pg 245, Abstract). The principal historical limitation of this vector system, efficiency of rAAV-mediated transduction, has been addressed by efforts to improve the titer, purity, and production capacity of rAAV preparations. RAAV transduction in certain tissues has been limited by the paucity of its receptors on certain cell types (pg 250, col. 1, ¶1). However, innovations have been made with regard to directing rAAV to attach to alternative receptors. (pg 250, col. 2, ¶1). Detailed studies of the AAV capsid proteins have shown that certain sites within the capsid can be intentionally altered to incorporate new targeting ligands. Theoretically, this procedure could be to target a wide variety of different receptors and thus substantially expand the cellular tropism.

Mah et al (Molecular Therapy 6(1):106-112, 2001) teach obstacles impairing the use of rAAV as gene therapy vectors include sub-therapeutic levels of transduction, which is affected by such factors as cellular receptor density, multiplicity of infection and the time of exposure to

vector particles, and the ability to target the site of gene transfer (pg 106, col. 1, ¶1). To this end, Mah et al teach the conjugation of microspheres to rAAV vectors to retard the flow of the vector through the vasculature, thus resulting in increased exposure time of vector to target cells (pg 106, col. 2, lines 4-7).

The prior art is silent with respect to the administration of agents, particularly the elected embodiments DOXIL® and LLnL, to enhance rAAV transduction. The claimed methods recite the administration of agents to alter distinctly different cell biological processes to enhance transduction. However, Goncalves (Virology J. 2: 43; 17 pages, 2005) teaches that the events and processes that regulate the trafficking of AAV particles into the nucleus are still not fully understood (pg 5 of 17). An increasingly important area in the development of AAV as a vector concerns the engineering of altered cell tropisms to narrow or broaden rAAV-mediated gene delivery and to increase its efficiency in tissues refractory to AAV2 infection. Cells can be poorly transduced by prototype rAAV2 not only because of low receptor content but also owing to impaired intracellular virion trafficking and uncoating or single-to-double strand genome conversion. Thus, considering that these processes depend either directly or indirectly on capsid conformation, cell targeting strategies determine not only the cell type(s) with which the vector interacts but also critically affect the efficiency of the whole gene transfer process. (pg 7 of 17) Several of these approaches rely on the modification by chemical, immunological or genetic means of the AAV2 capsid structure endowing it with ligands that interact with specific cell surface molecules. Another route to alter rAAV tropism exploits the natural capsid diversity of newly isolated serotypes by packaging rAAV2 genomes into capsids derived from other human or non-human AAV isolates. To this end, up until now, most researchers employ hybrid *trans*-complementing constructs that encode *rep* from AAV2 whereas *cap* is derived from the serotype displaying the cell tropism of choice. For example, experiments published recently using rAAV2 genomes pseudotyped with coats from AAV6 and AAV8 revealed stunning gene transfer efficiencies when these vectors were administered alone at high doses or in combination with a blood vessel permeating agent.

It is noted that Yan et al (J. Virology 78(6):2863-2874, 2004; *of record) teach that doxorubicin is an inhibitor of proteosome proteolytic activity, specifically the chymotrypsin-like proteolytic activity of the 20S proteosome (pg 2864, col. 1, ¶2; pg 2873, col. 2, lines 1-3), which contradicts the agent elected species recited in Claims 43 and 60, wherein the doxorubicin and DOXIL® are recited to not be an inhibitor of proteosome proteolytic activity.

Duan et al (J. Clin. Invest. 105:1573-1587, 2000; *of record) teach that the administration of tripeptide protease inhibitors, e.g. LLnL, increase rAAV gene delivery (pg 1573, Abstract). However, this phenomena is not universal in that the proteosome inhibitor did not affect transduction of skeletal or cardiac muscle, indicating that tissue-specific ubiquitination of viral capsid proteins interfere with rAAV-2 transduction.

Given the limited teachings in the art regarding the co-administration of two or more compounds designed to specifically alter particular cell biological processes to intentionally enhance rAAV transduction of an enormous genus of mammalian cell types *in vitro*, *ex vivo* and *in vivo*, one of ordinary skill in the art would reasonably conclude that a high degree of unpredictability regarding an *a priori* determination that any specific compound will enhance viral transduction. It necessarily follows that the art recognizes significant unpredictability for any two agents to yield an additive interaction to enhance viral transduction. Furthermore, there is a clear contradiction between the art and the instant specification regarding the biochemical properties of the doxorubicin and DOXIL® as per the inhibition of proteosome proteolytic activity.

The Existence of Working Examples and The Amount of Direction Provided by the Inventor

The method steps of the invention require the artisan to administer one or more compounds (or agents), wherein each compound is capable of fulfilling a recited function, namely i) alter cellular uptake of rAAV, ii) modulate rAAV processing in the cell, and iii) processing in intracellular compartments. Applicant broadly contemplates the term viral transduction to include endocytosis, trafficking and processing of the rAAV through intracellular compartment(s), e.g., endosomal compartments, decreased viral nucleic acid or protein degradation, increased viral uncoating, or increased nuclear transport of virus or the viral genome, agents that interact with cytoskeletal elements, e.g., microtubules or microfilaments (pg

8, lines 23-27). However, neither the claims nor the specification disclose explicitly which compound performs the recited function(s). For example, method Claims 4 and 46 recite the limitation "cellular uptake of rAAV" in reference to a cellular function modified by exposure to a second (Claim 46) or third (Claim 4) agent. There is insufficient antecedent basis for this limitation in the claim. The specification fails to use the phrase 'cellular uptake'. Thus, it necessarily follows that the specification fails to disclose specific agent compositions that can perform the claimed function. Rather, the specification discloses the phrases 'viral uptake' and "AAV uptake' (pg 75, lines 18-21). However, there are no specifically disclosed agents that alter 'viral uptake' besides LLnL and EGTA (pg 72, lines 10-15) so as to apprise the artisan exactly what agent is to be administered to fulfill the method step limitation(s).

The lack of correlation in the specification regarding the particular cell biological activity(ies) affected by each contemplated agent necessarily fails to provide sufficient guidance to the artisan so as to perform the claimed method(s). In the instant case, Applicant has elected the agent structure species "DOXIL®" and "LLnL", and the agent function species "alters cellular uptake of rAAV" and "modulates rAAV processing in the cell". The specification discloses DOXIL® to be a chemotherapeutic agent (pg 79, line 20) and is disclosed to enhance rAAV transduction (pg 82, line 31). DOXIL® is the liposomal formulation of doxorubicin (pg 80, line 17) that is an approved antibiotic (pg 9, line 25) and chemotherapeutic agent (pg 79, line 20). The specification also discloses that "LLnL" is a proteosome inhibitor that can enhance transduction (pg 5, line 30), but acts at a point distal to (that is, after) virus binding and entry (pg 70, line 8). LLnL and doxorubicin synergistically enhance rAAV transduction *in vitro*, as measured by reporter gene expression 1000-fold, while individually, doxorubicin and LLnL enhanced rAAV reporter gene expression 100- and 10-fold, respectively (pg 12, lines 8-10).

However, the instantly elected embodiment is DOXIL®, not doxorubicin. It is noted that DOXIL® could not be confirmed to be bioavailable to cell culture cells (pg 80, lines 17-18; pg 82, lines 2-4), and that "intranasally DOXIL®-treated mice did better than the doxorubicin-treated animals" (pg 110, lines 17-19). Thus, one of ordinary skill in the art would reasonably conclude that the functional ability(ies) of DOXIL® are not identical to doxorubicin, limiting the context in which DOXIL®l may be used in combination with another agent(s) to enhance rAAV transduction. The specification fails to disclose the *in vitro, ex vivo* or *in vivo* administration of

DOXIL® with any other agent, e.g. the elected LLnL embodiment, to a mammalian target cell. Thus, it naturally follows that there is no evidence that the co-administration of DOXIL® with LLnL will yield a functional interaction so as to additively enhance rAAV transduction of mammalian cells.

The Quantity of Any Necessary Experimentation to Make or Use the Invention

Thus, the quantity of necessary experimentation to make or use the invention as claimed, based upon what is known in the art and what has been disclosed in the specification, will create an undue burden for a person of ordinary skill in the art to demonstrate that the administration of an enormous genus of structurally and functionally diverse compositions so as to affect a broad genus of distinctly different and mutually exclusive cell biological processes will yield an additive functional interaction so as to enhance rAAV transduction of enormous genus of mammalian cells (both organisms and physiological cell types), wherein the transduction may occur *in vitro*, *ex vivo* or *in vivo*.

The instant portion of the invention, as claimed, falls under the "germ of an idea" concept defined by the CAFC. The court has stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may not be workable". The court continues to say that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genentech Inc v. Novo NordiskA/S* 42 USPQ2d 1001, at 1005). The claimed methods of enhancing rAAV transduction comprising contacting a mammalian cell with an enormous genus of structurally and functionally diverse compositions so as to affect a broad genus of distinctly different and mutually exclusive cell biological processes constitute such a "germ of an idea".

The courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application. 27 USPQ2d 1662 *Exparte Maizel*. In the instant case, in view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention.

10. **Claims 4-7, 28, 46 and 54 are rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

With respect to Claims 4 and 46, the claims recite the limitation "cellular uptake of rAAV" in reference to a cellular function modified by exposure to a second (Claim 46) or third (Claim 4) agent. There is insufficient antecedent basis for this limitation in the claim because the specification fails to use the phrase 'cellular uptake'.

With respect to Claims 5-7, the claims recited the limitation "corresponding" in reference to a mammalian cell that has been contacted with the rAAV and one or more agents. However, neither the claims nor the specification define the term "corresponding" so as to apprise the artisan the evolutionary and biological, i.e. physiological, relationship between the mammalian cell that is contacted and the mammalian cell that is not contacted. For example, does a hamster cell correspond to a human cell, or does a lung cell correspond to a glial cell?

With respect to Claims 28 and 54, neither the claims nor the specification define the term "rAAV processing" so as to inform the artisan exactly what cell biological activity must be modulated by the agent composition.

11. **Claims 1-2, 4-24, 28, 43-44, 46-50, 54 and 60 are rejected under 35 U.S.C. 112, second paragraph**, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the correlation between the identity and structural limitations of each composition/agent and the

recited cellular effect achieved by that agent. Claims 1, 4, 28, 43, 46 and 54 recite cellular functions achieved by one or more agents, but the identity of the agent that performs the function is not recited. Conversely, Claims 8, 21, 47 and 60 recite several agents, but the function each agent performs in the target cell so as to achieve the inventive method is not recited. Dependent claims are included in the basis of the rejection because although they recite and encompass the method of using one or more agents, they do not clarify the nature of which agent performs which activity.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. **Claims 43, 47, 50, 54 and 60 are rejected under 35 U.S.C. 102(a)** as being anticipated by Schwarzbach et al (Int. J. Oncology 20: 1211-1218, 2002).

The claims are drawn to a method to enhance rAAV transduction of a mammalian cell, the method comprising contacting the mammalian cell with at least one rAAV and at least one agent, with the proviso that the agent is not an inhibitor of proteosome proteolytic activity.

Schwarzbach et al teach the administration of doxorubicin and recombinant AAV-2 viruses to thirteen human sarcoma cell lines (pg 1212, Materials and Methods), wherein the art recognizes doxorubicin to be an antibiotic and chemotherapeutic.

With respect to the functional limitations of agent recited in Claims 43 and 54, Schwarzbach et al do not teach the doxorubicin to modulate rAAV processing in the cell. However, given the disclosure of the instant application, the doxorubicin would inherently possess the recited functional properties at the time of Schwarzbach et al, as there is nothing of

record to distinguish the doxorubicin of Schwarzbach et al from the doxorubicin of the instant application.

Thus, Schwarzbach et al anticipate Claims 43, 47, 50, 54 and 60.

13. **Claims 43, 47, 50, 54 and 60 are rejected under 35 U.S.C. 102(b)** as being anticipated by Yalkinoglu et al (Int. J. Cancer 45(6): 1195-1203, 1990, Abstract only).

Yalkinoglu et al teach the administration of adriamycin (also known as doxorubicin) and adeno-associated virus 2 on Chinese hamster ovary (CHO) cells.

With respect to the functional limitations of agent recited in Claims 43 and 54, Yalkinoglu et al do not teach the doxorubicin to modulate rAAV processing in the cell. However, given the disclosure of the instant application, the doxorubicin would inherently possess the recited functional properties at the time of Yalkinoglu et al, as there is nothing of record to distinguish the doxorubicin of Yalkinoglu et al from the doxorubicin of the instant application.

Thus, Yalkinoglu et al anticipate Claims 43, 47, 50, 54 and 60.

14. **Claims 1-2, 5-7, 9, 16, 18, 21-23, 28, 43-44, 46, 48, 50 and 54 are rejected under 35 U.S.C. 102(b)** as being anticipated by Duan et al (J. Clin. Invest. 105:1573-1587, 2000; *of record).

The claims are drawn to methods of enhancing recombinant adeno-associated virus (rAAV) transduction of a mammalian cell, the method comprising contacting the mammalian cell with at least one rAAV and at least one (Claim 43) or at least two (Claim 1) agents in an amount effective to enhance rAAV transduction.

To the extent that neither the instant specification nor the instant claims define the correlation between the identity and structural limitations of each composition/agent and the recited cellular effect achieved by that agent, the following rejection is applied.

With respect to Claims 1, 43, 46, Duan et al teach a method of enhancing adeno-associated virus 2 (rAAV-2) transduction of human airway epithelial cells, the method

comprising contacting the cells with rAAV, a first agent that is EGTA that has been shown to increase AAV transduction from the apical surface by seven- to ten-fold (pg 1580, col. 2, last 6 lines), and a second agent that is the tripeptide protease inhibitor LLnL, wherein the combined administration of EGTA and LLnL is greater than either agent alone (pg 1576, Figure 5).

With respect to Claims 2, 9, 18 and 44, Duan et al teach the AAV vector to comprise a marker gene, specifically Green Fluorescent Protein (GFP) (pg 1574, Methods, see also references cited therein).

With respect to Claims 5-7, Duan et al teach the agents enhanced transduction by at least 10 fold (pg 1576, Figure 5).

With respect to Claims 16, 22, 48 and 50, Duan et al teach the cell to be human airway (lung) epithelial cells.

With respect to Claim 21, Duan et al teach one of the agents to be LLnL.

With respect to Claim 23, Duan et al teach that the cells are contacted with at least one agent (EGTA) before the cell is contacted with the virus (pg 1576, Figure 5, legend).

With respect to Claims 28 and 54, Duan et al teach that at least one of the agents (LLnL) modulates rAAV processing in the cell (pg 1582, col. 1, lines 5-7; col. 2, lines 15-17).

Thus, Duan et al anticipate Claims 1-2, 5-7, 9, 16, 18, 21-23, 28, 43-44, 46, 48, 50 and 54.

15. **Claims 1-2, 4-7, 9, 18, 22, 28, 43-44, 46, 50 and 54 are rejected under 35 U.S.C. 102(b)** as being anticipated by Tenenbaum et al (Gene Therapy 6: 1045-1053, 1999).

The claims are drawn to methods of enhancing recombinant adeno-associated virus (rAAV) transduction of a mammalian cell, the method comprising contacting the mammalian cell with at least one rAAV and at least one (Claim 43) or at least two (Claim 1) agents in an amount effective to enhance rAAV transduction.

To the extent that neither the instant specification nor the instant claims define the correlation between the identity and structural limitations of each composition/agent and the recited cellular effect achieved by that agent, the following rejection is applied.

Tenenbaum et al teach a method of enhancing rAAV transduction of HeLa cells (human) comprising contacting the mammalian cell with rAAV encoding the marker gene Green Fluorescent Protein (GFP), wildtype AAV and sonicated crude lysates of cells previously infected with rAAV (pg 1046, Figure 2; pg 1048, Enhancement of transduction), wherein one of ordinary skill in the art recognizes that sonicated crude cell lysates comprise more than one agent. The transduction efficiency improved to 40% as compared to the efficiency of purified virus alone (0.6%). To the extent that neither the claims nor the specification define the term "rAAV processing" so as to inform the artisan exactly what cell biological activity must be modulated by the agent composition, absent evidence to the contrary, it is the Examiner's position that the wildtype AAV and at least one composition present in the crude cell lysate modulate rAAV processing in the cell.

Thus, Tenenbaum anticipate Claims 1-2, 4-7, 9, 18, 22, 28, 43-44, 46, 50 and 54.

Conclusion

16. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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